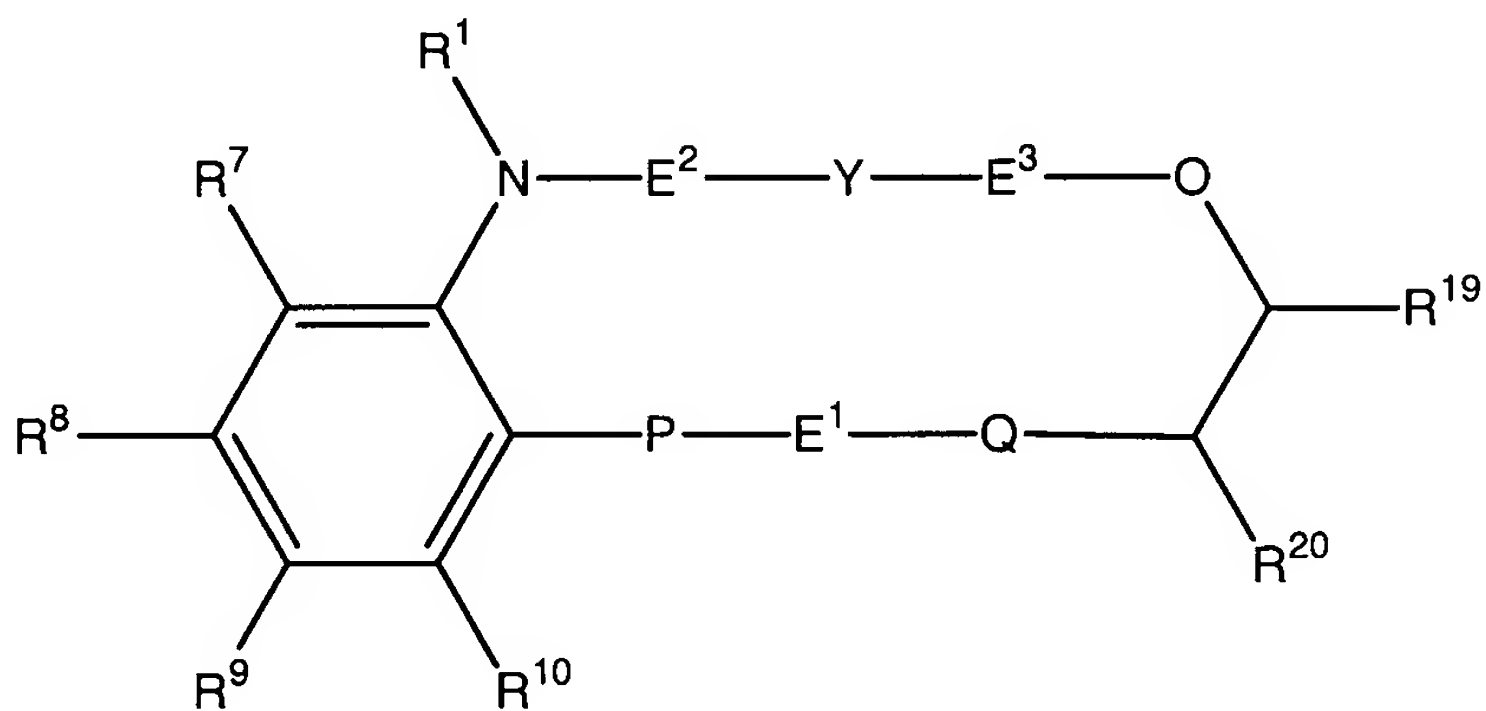


REMARKS

The Claimed Invention

The present invention is directed to derivatives of crown ether compounds that optionally comprise a dye, a reactive group or a conjugated substance. These crown ether compounds have the following general structure:



wherein the substituents are as defined in the claims. The present crown ether compounds bind sodium, calcium, potassium ions and other ions under physiological conditions and when attached to a fluorophore demonstrate a changed fluorescent signal when bound to the ions. Thus, these crown ether compounds find particular use as indicators of the metal ions.

The Pending Claims

Prior to entry of the attached amendments, Claims 1-38 are pending. Claims 1-27 are directed to the present crown ether compounds. Claims 28-29 are directed to a composition comprising a present crown ether compound and a metal ion. Claims 30-37 are directed to a method for detecting target metal ions in a sample using the present crown ether compounds. Claim 38 is directed to a kit for binding a metal ion in a sample.

The Office Action

Claims 1-27 are rejected.

Claims 28-38 are withdrawn from consideration.

Claims 1-27 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention.

Amendments

No claims were amended or cancelled.

RESPONSE TO THE ELECTION REQUIREMENT

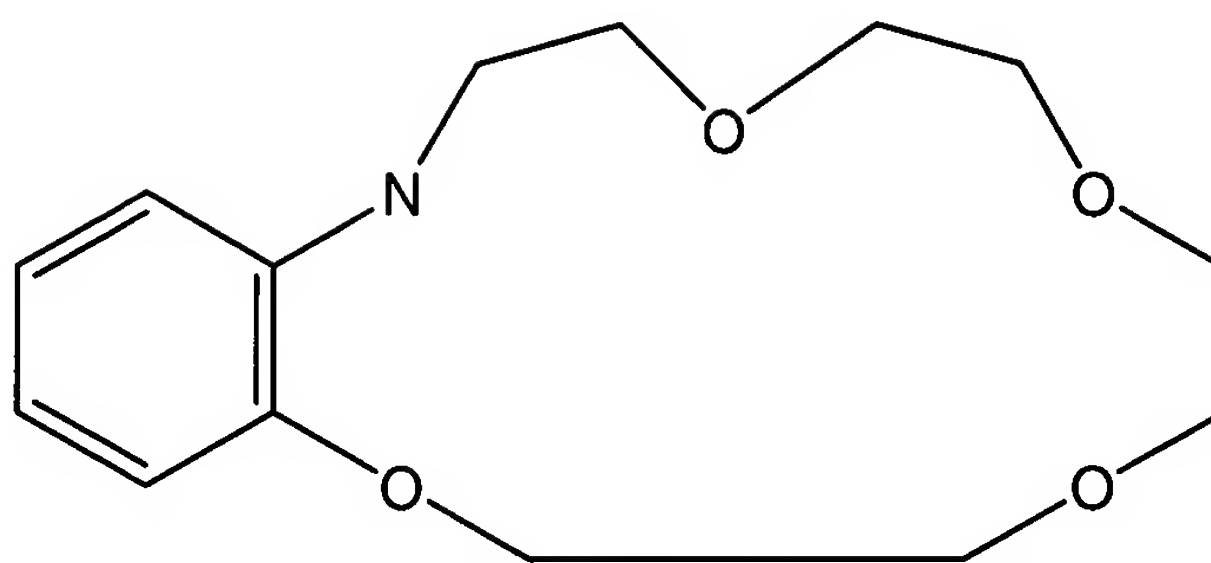
In the response that follows, the Examiner's Election/Restriction of the Applicant's claimed invention is provided in full text, as identified by indented small bold print, followed by the Applicants response.

Applicant's election of compound 86 on pages 96-97 in the reply filed on 07/17/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants respectfully point out that there was no restriction requirement made by the Examiner in the Office Action mailed 07/12/05, only an election requirement. MPEP 803.1 states that when issuing a restriction requirement "Examiners must provide reasons and or reasons to support conclusions". The Examiner did not split the claims up into groups based on what he believed to be the supposed separate inventions or provide any statement as to why supposedly there is more than one invention present in the current claims set. Thus, there was nothing for the Applicant to "distinct and specifically point out to be the supposed errors in the restriction requirement" as there was no restriction requirement. However, the applicants did state that the election was traversed.

As required by 35 U.S.C. 121 Applicants elected a species for the *purposes of initiating a search and examination*. Thus, an election was made with a request by the Applicants for the Examiner to examine all of the claims.

The elected compound was not found in the search and is allowable. The search has been expanded to embrace the core



Compounds embraced by this core are under consideration. The search did not extend to compounds wherein Sc is as defined in claims 8 and 9 because these biomolecules require separate searches. Should applicants maintain these groups, a restriction requirement will be made to elect a specific Sc group.

Claims 28-38 (along with subject matter not falling under the above core) are withdrawn from consideration because they are drawn to compositions, methods and kits that raise different issues of patentability and require separate searches.

Applicants respectfully request the Examiner to provide reasoning as to why he believes the method, composition and kit claims are patentably distinct from the compound claims and from the method claims, as none has been provided, demonstrating that the inventions are independent or distinct as claimed and that there is a serious burden on the Examiner to perform search and Examination of the current claims 1-38. As such, Applicants do not believe a proper restriction requirement has been made and object to Claims 28-38 being withdrawn. Applicants respectfully request that these claims be rejoined with Claims 1-27 or provide adequate reasoning as to why the withdrawn claims are independent inventions.

Applicants respectfully request that the Examiner apply the same methodology that was applied in the prosecution of the parent case, US Serial No. 10/026,302. In this instance a core structure was elected, subsequently found patentable and then all claims the included the patentable compound limitation (methods, compounds, kits compositions) were examined and subsequently allowed. In that case the examiner stated “Compounds, corresponding compositions, a method of use and a process of making that are of the same scope are considered to form a single inventive concept.”

RESPONSE TO THE REJECTIONS

In the response that follows, the Examiner's individual rejections are provided in full text, as identified by indented small bold print, followed by the Applicant's response.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention.

This rejection is respectfully traversed because the following terms are properly defined in the specification. These claim terms must be examined in view of 1) the content of the present application, 2) the teachings of the prior art, and 3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP 2173.02). The Applicants assert that, in view of these criteria, the claim terms "a reactive group", "conjugated substance" and "a reporter molecule" are properly defined in the present application.

- i) **The group Rx is defined as "a reactive group." This is indefinite because a "reactive group" depends on the reaction condition and changes definition depending on where it is used. Applicants are requested to insert the actual groups intended. The groups at claims 6 and 7 need to be presented as radicals and not as classed of compounds.**

Applicants respectfully traverse this rejection because the reactive groups (Rx) are clear.

A chemically reactive group is a term well known in the art (See, R. Haugland, MOLECULAR PROBES HANDBOOK OF FLUORESCENT PROBES AND RESEARCH CHEMICALS, Chapters 1-3 (1996)). Such a group generally represents a point of attachment for another substance and means a group that is capable of reacting with another chemical group to form a covalent bond. Some require no other reactants for the reaction to occur, for example, the reaction of a succinimidyl ester of a carboxylic acid with an amine. However, some reactive groups, such as carboxylic acid, do

typically require activation before a reaction will take place that forms a covalent bond (See, the note on the bottom of table 2 on page 42) with another substance to form a dye-conjugate of the present invention. Not all chemical groups are capable of readily reacting with another chemical group. In fact, many chemical groups are inert under many reaction conditions. Because of these reactive group properties, and because these are common terms used in the art, it is not necessary, or feasible, to define all the groups, that are *not* reactive groups but rather it is more important to define *what* constitutes a reactive group.

The present application defines "reactive group" to be a group that facilitates coupling of a present crown ether compound to "a wide variety of organic or inorganic substances that contain or are modified to contain functional groups with suitable reactivity, resulting in chemical attachment of the conjugated substance (Sc)" (page 40 lines 13-15). These moieties capable of chemically reacting with a group on another compound are specifically disclosed in the specification to constitute three species: 1) a nucleophile (page 40, line 16), 2) an electrophile (page 40 line 16), or 3) a photoactivatable group (page 40 line 117). An appropriate nucleophile and electrophile will spontaneously react with each other to form a covalent linkage and a photoactivatable group will react with an appropriate group on another compound when activated with an appropriate wavelength to form a covalent bond.

A nucleophile is a term well known in the art and is generally understood to mean a negative ion or a molecule that has an unshared pair of electrons. More simply stated, nucleophiles are electron-pair donors. Furthermore, it is understood in the art that during a chemical reaction a nucleophile attacks an electron deficient center of another molecule or a positive ion, i.e. an electrophile. An electrophile is also a term well known in the art and is generally understood to mean a positive ion or an electron-accepting group. The present specification provides an extensive table of nucleophiles and electrophiles (reactive groups) that will react with each other and the resulting covalent bonds that are formed (See, Table 3 page 40-42).

Therefore, Applicants respectfully assert that the specification properly defines the claim term "reactive group". Applicants respectfully request that the Examiner withdraw this rejection of Claims 1-27.

Furthermore, Applicants respectfully assert that the reactive groups (Rx) are like any other R group, chemical moieties that may be attached to the core structure at the sites specified by the R groups. The R groups specifically claimed in the independent claims can be attached to the core structure at any of the specified R groups in the claims.

- ii) **The group Sc is defined as a “conjugated substance.” One of skill in the art cannot say what the metes and bounds of this group are.**

The present specification discloses “compounds incorporating a reactive group (Rx) can be coupled to a wide variety of organic and inorganic substances that contain or are modified to contain functional groups with suitable reactivity, resulting in chemical attachment of the conjugated substance (Sc)” (page 40 lines 12-15). Thus, a conjugated substance is broadly defined to mean an organic or inorganic substance that contains a reactive group wherein the reactive group will form a covalent bond with the *present compounds* that contain an appropriate reactive group. Inorganic and organic substances are terms well known in the art and reactive group is defined by the present specification. It is generally understood that a chemical reaction between a nucleophile and an electrophile results in a covalent bond; thus, Applicants respectfully assert that this claim term, “conjugated substance”, is not considered ambiguous.

The present specification provides numerous preferred embodiments of conjugated substances (page 43 line 16 to page 44 line 20). Many of these preferred embodiments are specifically claimed in the claims (See, Claims 8, 9 and 23). These claims clearly define the metes and bounds of a conjugated substance. The Examiner is respectfully requested to withdraw this rejection of Claims 1-27 in view of the claim term “conjugated substance”.

- iii) **The group DYE is defined as “a reporter molecule.” This is manifestly indefinite because one skilled in the art cannot say what this is. First, a molecule does not have an open valency to bond as a radical to the rest of the macrocycle. Secondly, it is not known what is and is not a reporter molecule. The compounds at claim 10 cannot be radicals because they do not have a point of attachment. Appropriate correction is required.**

Applicants respectfully traverse this rejection because the specification properly defines the term “reporter molecule”. The specification states that the DYE moiety of the present invention functions as a reporter molecule to confer a detectable signal to the target ions” (page 18 line 37: page 19 lines 1-2). The specification defines the term “DYE” functionally as “any chemical moiety that exhibits an absorption maximum beyond 320 nm, that is bound to the crown chelate by a covalent linkage L, or is fused to the crown chelate” (page 19 lines 25-26). The specification further limits this definition by stating “the dye moiety includes without limitation a fluorophore, a chromophore, a fluorescent protein and an energy transfer pair” (page 19 lines 4-5). Thus, the specification functionally defines “DYE” and then further defines the DYE to be a fluorophore, a chromophore, a fluorescent protein and an energy transfer pair.

Based on this definition it is clear to one of skill in the art what is a DYE or reporter molecule. However the specification further teaches that the DYE moiety typically contains one or more aromatic or heteroaromatic rings that are optionally substituted one or more times by a variety of substituents (page 21 lines 16-20). Thus, the chromophores or fluorophores that are the DYE moiety typically contain an aromatic ring, yet another distinguishing feature that provides limits of the DYE moiety. Furthermore, the specification provides examples of known DYE moieties (page 20-22, See Table 2).

Thus, the presently claimed DYE moiety has been defined functionally with additional physical and structural limitations. Numerous known and unknown DYE moieties when covalently attached to the present crown ethers form chromogenic or fluorogenic ion indicators. The DYE moiety is not intended to be limiting, as many different moieties will work with the present invention. Therefore, Claim 1 read in view of the specification clearly defines what is a DYE moiety. Applicants respectfully request that this rejection of Claim 1 in view of reporter molecule be withdrawn.

As stated above for reactive groups, the reporter molecule is like any other R group, chemical moieties that may be attached to the core structure at the sites specified by the R groups. The R groups specifically claimed in the independent claims can be attached to the core structure at any of the specified R groups in the claims.

Applicants respectfully request that the Examiner withdraw this rejection of Claims 1-27 based on the Claim term “reactive group”, “conjugated substance” and “reporter molecule” because 1) one of ordinary skill would know what was intended by these claim terms, 2) these claim terms are adequately defined by the present specification and 3) the terms are commonly used in analogous art references. Furthermore, many of the claims contain preferred reactive groups, conjugated substances and reporter molecules.

INFORMATION DISCLOSURE STATEMENT

In the response that follows, the Examiner's individual comments are provided in full text, as identified by indented small bold print, followed by the Applicant's response.

The information disclosure statement filed 11/04/03 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. The references C1-C5 are not present in this case or the parent application. A line has been drawn through these citations.

Applicants have enclosed a copy of original cited C1-C5 references with this response along with a completed substituted 1449 form.

The enclosed references may be material to the examination of the above-identified application. Applicants, respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. The Examiner is requested to initial and return the enclosed PTO-1449 form in accordance with MPEP §609.

This Information Disclosure Statement pursuant to 37 CFR 1.97 is not to be construed as a representation that: (1) a search has been made; (2) the above information constitutes prior art to the subject invention. Accordingly, it is requested that the Examiner consider the enclosed references.

CONCLUSION

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (541) 335-0203.

Respectfully submitted,

Date: October 25, 2005

Koren J. Anderson
Koren J. Anderson, Ph.D.
Reg. No. 51,061

Molecular Probes, Inc. (A wholly owned subsidiary of Invitrogen Corp.)
29851 Willow Creek Rd.
Eugene, Oregon, 97402
Phone: (541) 335-0203
Facsimile: (541) 335-0354